PATENT COOPERATION TREATY

PCT

10/575804

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P70604WO00GP	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/033818	International filing date *(day/month/year)* 13 October 2004 (13.10.2004)	Priority date *(day/month/year)* 13 October 2003 (13.10.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GENACO BIOMEDICAL PRODUCTS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 September 2006 (19.09.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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BIRMINGHAM, AL 35203-2104

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	11 AUG 2006
Applicant's or agent's file reference P70604WO00GP	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/33818	13 October 2004 (13.10.2004)	13 October 2003 (13.10.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC: **C12Q 1/68**(2006.01)
USPC: 435/6

Applicant

GENACO BIOMEDICAL PRODUCTS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	14 July 2006 (14.07.2006)	Mark Staples Telephone No. (571) 272 0700

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/33818

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 18-21

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 18-21 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 18 and dependent claims 19-21 are indefinite and hence unsearchable for recitation of "a selective amplification process:" in claim 18. What is to be selected and what is to be amplified are not defined. The steps for this process are also omitted. There is no antecedent basis for this process. Claims 18-21 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT article 6; no meaningful opinion could be formed.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-17 and 22-36

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 4-7, 12, 17, and 35	YES
	Claims 1-3, 8-11, 13-16, 22, 23, 28-34, and 36	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-17, 22, 23, and 28-26	NO
Industrial applicability (IA)	Claims 1-17, 22, 23, and 28-36	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 18-21 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT article 6 because claim 18 is indefinite for the following reasons: the recitation of "a selective amplification process" in claim 18. What is to be selected and what is to be amplified are not defined. The steps for this process are also omitted. There is no antecedent basis for this process. Thus claims 18 and dependent claims 19-21 are indefinite and unsearchable.

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-3, 8-11, 13-16, 22, 23, 28-34, and 36 lack novelty under PCT Article 33(2) as anticipated by Chen (22.05.2003).

Regarding claims 1-3, 22, 23, and 28 Chen teaches multiplex PCR (primer based amplification) using a first round of amplification "of: carrying out a first round of PCR amplification with at least one primary primer specific for one locus on one strand of DNA in said sample" (see claim 10). It is noted that this encompasses the use of two primer pairs for the first amplification in claim 1 and three or more primers of claim 22 of the instant application. Chen further teaches a second round of amplification "with at least one secondary primer having a second homologous portion" (see claim 10) and as illustrated in Figure 1. It is noted that this encompasses the second amplification of claim 1 and the two or more target amplification primers of claim 23 of the instant application. It is especially noted that the structure for detection by Chen which is the secondary primer, no. 10, with labeled complement, no. 20, in Figure 1 encompasses the structure for detection in the instant application which is the secondary primer, Rin, with labeled complement, RSP, in Figure 1A. These two structures have the same elements. It is further noted that claim 28 of the instant application relays that the label is on at least one of RSP or FSP.

Regarding claims 8 and 9 in the instant application, Chen teaches primary primers (target enrichment primers) at low concentrations of about 0.1 nM to about 0.5 nM (about 0.0001 to about 0.0005 uM) and secondary primers (target amplification primers) at a high concentrations, e.g., about 25nm to about 50 nm (about 0.025 to about 0.05 uM), see paragraph 0061 on p. 6. The upper regions of each of these ranges, being approximate, fall within the low and high ranges of claim 9.

Regarding claims 10 and 11 in the instant application, Chen teaches limited cycling, that is not exponential cycling, on the first amplification and teaches that the primers on the first amplification are in an equal amount (see claims 10 and 11).

Regarding claim 13 in the instant application, Chen teaches a secondary primers each having the same concentration of 100 nM (See p. 12, paragraph 0105).

Regarding claims 14 and 15 in the instant application, Chen teaches a secondary primer SC_5, SEQ ID NO. 2, (target amplification primer) at 50 nm which is a higher concentration than another secondary primer SC 4, SEQ ID NO. 1, at 25 nM. The primer, SEQ ID NO. 2, at the higher concentration was labeled for detection with BODIPY_TAMRA. (See p. 7, Methods, paragraph 0072).

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

Regarding claim 16 in the instant application, Chen teaches the first and second amplifications each comprising at least two complete cycles (see p. 7 paragraph 0072 with the first amplification being 10 cycles and the second being 25 cycles).

Regarding claims 28-34 and 36 in the instant application, Chen teaches the method of detecting target sequences by the direct method of fluorescent dye labels and indirect method of enzyme label (see entire application, especially claims 3 and 4, paragraph 0016 on p. 2, and Figure 1).

Claims 4-7 lack an inventive step under PCT Article 33(3) as being obvious over Chen (22.05.2003) in view of Qiagen (2002). Chen teaches primers of different lengths and the length of primers being different for primary and secondary amplifications. Chen teaches primers ranging from 20 to greater than 40 nucleotides (see Table 1 on p. 8). Chen does not teach the exact primer length ranges given of claims 4-7. Qiagen teaches standard primers range from 18-30 nucleotides which encompasses the ranges of claims 4-7 (see Table 12 on p. 30). Thus it would have been obvious to one of ordinary skill in the art to use primers of different lengths of Qiagen for different primer lengths of primary and secondary amplifications.

Claims 12 lacks an inventive step under PCT Article 33(3) as being obvious over Chen (22.05.2003) in view of Qiagen (2002). Chen teaches primary primers at the same concentration and that this concentration can vary. Chen does not specifically teach at least one of the primary primers (target enrichment primers) being at a different concentration. Qiagen teaches that primer concentrations can be varied individually (entire Handbook, esp. Troubleshooting pp. 24-27, more especially step 4 on p. 24 and step 7 on p. 27). Thus it would have been obvious to one of ordinary skill in the art to vary the concentrations of individual primary primers.

Claim 17 lacks an inventive step under PCT Article 33(3) as being obvious over Chen (22.05.2003) in view of Qiagen (2002). Chen teaches conditions of amplication and modification of those conditions (see entire application and, for example, p.3 paragraph 030 and p. 9 paragraph 081). Chen does not teach the exact conditions of claim 17. Qiagen teaches various conditions of amplification and that these can conditions can be optimized (see entire Handbook, especially p. 6 Table 2 step 6). Thus it would have been obvious to one of ordinary skill in the art to use different conditions, than those specifically given by of Chen, for amplification.

Claim 35 lacks an inventive step under PCT Article 33(3) as being obvious over Chen (22.05.2003) in view of Cheung (1993). Chen teaches various labels for DNA detection. Chen does not teach fluorescent microphores of claim 35. Cheung teaches fluorescent microspheres for detection of DNA (see Abstract). Thus it would have been obvious to one of ordinary skill in the art to use fluorescent microspheres for detection of DNA in the detection method of claim 35.

Claims 1-17, 22, 23, and 28-36 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.